

# UC Berkeley

## UC Berkeley Previously Published Works

### Title

Modelling environmentally-mediated infectious diseases of humans: transmission dynamics of schistosomiasis in China.

### Permalink

<https://escholarship.org/uc/item/9393r6w7>

### Author

Remais, Justin

### Publication Date

2010

### DOI

10.1007/978-1-4419-6064-1\_6

Peer reviewed

## CHAPTER 6

---

# Modelling Environmentally-Mediated Infectious Diseases of Humans: Transmission Dynamics of Schistosomiasis in China

Justin Remais\*

### Abstract

Macroparasites of humans are sensitive to a variety of environmental variables, including temperature, rainfall and hydrology, yet current comprehension of these relationships is limited. Given the incomplete mechanistic understanding of environment-disease interactions, mathematical models that describe them have seldom included the effects of time-varying environmental processes on transmission dynamics and where they have been included, simple generic, periodic functions are usually used. Few examples exist where seasonal forcing functions describe the actual processes underlying the environmental drivers of disease dynamics. Transmission of human schistosomes, which involves multiple environmental stages, offers a model for applying our understanding of the environmental determinants of the viability, longevity, infectivity and mobility of these stages to controlling disease in diverse environments. Here, a mathematical model of schistosomiasis transmission is presented which incorporates the effects of environmental variables on transmission. Model dynamics are explored and several key extensions to the model are proposed.

### Introduction

A common feature of many of the most debilitating macroparasites of humans is their dependence on environmental life-stages subject to dynamic climatic, ecological, hydrological and other conditions. This phase can be wholly environmental, where for example infected humans excrete parasite eggs in feces and others are exposed via contaminated food or, as in the case of hookworm, where contact with contaminated soil can result in penetration of the parasite through the intact skin. Alternatively, the environmental phase may consist of time spent in an intermediate host, such as a snail or fish, itself subject to heterogeneous environments. Transmission of human schistosomes involves environmental phases of both types and thus understanding the environmental determinants of the viability, longevity, infectivity and mobility of these phases is key to conceptualizing disease transmission and ultimately controlling disease in diverse environments.

Schistosomes enter the environment as eggs that hatch in water into a free-swimming miracidium that seeks a snail of the appropriate species to infect. Asexual reproduction in the snail produces cercariae, another free-swimming aquatic stage with a lifespan on the order of a day, which penetrate the intact skin of a definitive host and mature into adult worms. The worms sexually pair and the female lays copious numbers of eggs that are the source of

---

\*Justin Remais— Rollins School of Public Health, Department of Environmental and Occupational Health, Emory University. Atlanta, Georgia. USA. Email: justin.remais@emory.edu

pathogenic response in the host. Some of these eggs find their way into the feces or urine, are excreted and the cycle begins again. The intermediate host, a freshwater snail and the two free-living aquatic stages are known to be subject to environmental stresses such as temperature<sup>1</sup> and shear forces present in the water column.<sup>2</sup> For *S. japonicum*, the species that causes schistosomiasis in east and southeast Asia, transmission is further complicated by the fact that a variety of mammals can serve as the definitive host,<sup>3</sup> including rodents, dogs, cats, pigs and water buffalo, the latter of which is particularly important to sustaining transmission in the lower Yangtze environment.<sup>4</sup>

In China, considerable progress has been made since the 1950s controlling transmission of *S. japonicum* in humans and domestic animals. From a total of 433 endemic counties in 1959, the disease has been eliminated from 260 counties leaving approximately 800,000 infected people and another 60 million at risk.<sup>5,6</sup> However, these represent only a small fraction of the worldwide total of schistosomiasis cases that the World Health Organization estimates at 200 million, 85% of which are in Africa.<sup>7</sup> Most of these infections are suffered by poor people, particularly children and most are preventable and treatable, although effective vaccines remain a hope for the future.

Where schistosomiasis transmission has been eliminated, targeted environmental modifications have often played an important role.<sup>8</sup> Conversely, major environmental changes such as water development projects have often led to a sustained elevating effect on schistosomiasis prevalence.<sup>9</sup> The underlying mechanisms shaping this relationship are poorly understood. An expansion in the preferred habitat of intermediate host snails is often implicated in these prevalence increases, yet few data exist to fortify this claim.<sup>10</sup> In China, recent evidence points to the influence of changing water levels on intermediate host populations.<sup>11</sup> Yet a clear mechanistic understanding of the processes that lead to increased disease is lacking and therefore opportunities to mitigate the disease impact of water projects using engineering or design principles is limited.<sup>12</sup>

Schistosomes are not alone among disease systems where mechanisms bridging environmental factors and epidemiological parameters have been poorly characterized. For example, although it has been well established that meningococcal meningitis in western Africa exhibits seasonal patterns, the particular causes remain uncertain and could range from low humidity to wind speed.<sup>13</sup> Similarly, multiple drivers have been proposed for the seasonal nature of cholera, including rainfall, temperature and planktonic blooms. Yet the specific roles of these drivers have not been resolved and well-established dynamic features, such as the second cholera peak experienced in endemic regions in south Asia, have gone largely unexplained.<sup>14</sup>

Given the limited mechanistic understanding of environment-disease interactions, mathematical models that describe them have seldom included the effects of time-varying environmental processes on transmission dynamics. Where they have been included, seasonality is commonly incorporated phenomenologically, using mathematical functions that are periodic in time and therefore describe in a generic way the seasonal variation in a parameter—a simple sinusoidal function is a common example. Few examples exist where seasonal forcing functions describe the actual processes underlying the environmental drivers of disease dynamics.<sup>15</sup> Because models that incorporate seasonality are sensitive to which parameters are externally forced as well as the shape of their forcing, there is a pressing need to identify the actual mechanisms at play. These mechanisms can include seasonal behaviors of definitive hosts, environmental forcing of vectors and intermediate hosts, sensitivities of parasite survival in the environment and annual variation in host births and deaths.

Understanding the mechanisms that tie environmental change to changes in disease dynamics is crucial for the development of comprehensive control strategies that may be more sustainable and cost effective in the long run. For the case of West Nile virus, for example, simulation studies have suggested that concentrating pesticide spraying efforts during the spring, when most transmission occurs among birds, could be more effective than the current practice of spraying in response to human cases in the late summer and early fall when mosquito numbers

are already in decline.<sup>16</sup> Ultimately, models and management practices that incorporate the timing of key events such as intermediate host reproduction and parasite development are essential to developing more successful control strategies. Understanding these mechanisms is also vital for estimating the long-term impact of impending climate change at global and regional scales on environmentally mediated diseases, whereas current projections are, to a large extent, empirically-based. Indeed, it has been argued in the case of malaria, for example, that models which are mechanistic, based on plausible underlying drivers of the system and basic biology, rather than empirical relationships, are more useful for predicting and responding to, the influence of climate change.<sup>17</sup>

Table 1 summarizes the evolution from simple deterministic models, to complex spatially-explicit, individually-based models appropriate for studying re-emergent scenarios in the Sichuan environment, where connectivity and environmental heterogeneity structure the dynamics of transmission. Iterative evaluation of alternative models in the light of field data is the essence of the modelling process in the application presented here. Below I summarize a model of schistosomiasis transmission in western China which aims to incorporate mechanistic environment-parasite relationships, in the hopes of understanding the local determinants of transmission and its control in endemic settings. Spatial extensions to the model are discussed and an alternative, stochastic framework is proposed for application to re-emergent disease.

## Modelling Schistosome Transmission

The use of mathematical models in the study of schistosomiasis dates back to the 1960s, when a four-parameter model was first proposed and used to explain the dynamics of endemic disease.<sup>18,19</sup> Since then, a number of models have been developed and used to explore the biological and epidemiological characteristics of schistosome species and their hosts, with a majority of them focused on *S. mansoni* and *S. haematobium*<sup>20-28</sup> and a few on *S. japonicum*.<sup>29,30</sup> This literature has three notable characteristics, it is explanatory rather than predictive, it is focused on phenomenological and, thereby, generalizable aspects of disease transmission and, for the most part, it has relied on analytical rather than computational methods of analysis. Koopman<sup>31</sup> has written of the successes and limitations of these models in general and where they fit into a more comprehensive mathematical approach. Thus far, these models have had a very limited impact on field studies and control programs.<sup>27,32</sup> One reason for this is the difficulty in adapting models to site-specific conditions, such as local climatic factors and intermediate host dynamics.

To date, we have used a model<sup>33</sup> of schistosomiasis transmission for our work in China with tactical rather than strategic objectives. Our focus is on site-specific transmission and the issue of selecting from the limited array of feasible control modalities that are effective and sustainable in a particular village. This is because Chinese experience, as well as our recent investigations, has clearly shown considerable variability in the prevalence and intensity of human infection in villages with similar agriculture but that are geographically proximate.<sup>34</sup> Hence, we regard the model as a platform for the synthesis of general knowledge of the mechanisms of disease transmission, quantitative estimates of biological parameter values and the local factors influencing transmission. To that end, the model has been extended to incorporate additional phenomena and additional data. Here, I build on the underlying model structure and parametrization described elsewhere,<sup>33</sup> incorporating the influence of additional environmental phenomena.

## The Model

The structure of the delay-differential equation model is shown schematically in Figure 1. Three state variables are tracked in the model, worm burden in each risk group, the density of susceptible snails in each environment and the density of infected snails in that environment. Here risk group refers to occupational subgroups known in this region to exhibit pronounced differences in the timing, intensity and location of water contact and corresponding infection levels, including farmers, students and others, the latter including domestic workers, teachers,

**Table 1. The evolution of modelling frameworks for *Schistosoma japonicum* transmission in Sichuan, China**

	Deterministic			Stochastic		
	Single-Population Model	Multi-Risk Group Model	Multi-Risk Group Model	Individual-Based Model	Spatially-Explicit Individual-Based Model	
Heterogeneous populations	No	Somewhat	Somewhat	Yes	Yes	
Assumption-free worm aggregation process	No	No	No	Yes	Yes	
Stochastic parasite introduction	No	No	Yes	Yes	Yes	
Spatial heterogeneity <sup>a</sup>	No	No	No	No	Yes	
Model complexity	Simple	Moderate	Moderate	Complex	Complex	
Suitable for studying control in endemic areas	Fair	Good	Not appropriate	Not appropriate	Not appropriate	
Suitable for studying emergence	Fair	Fair	Good	Good	Good	

<sup>a</sup>While both deterministic and stochastic models have the potential to be spatially-explicit, stochastic models of individuals interacting in space provide additional fidelity.

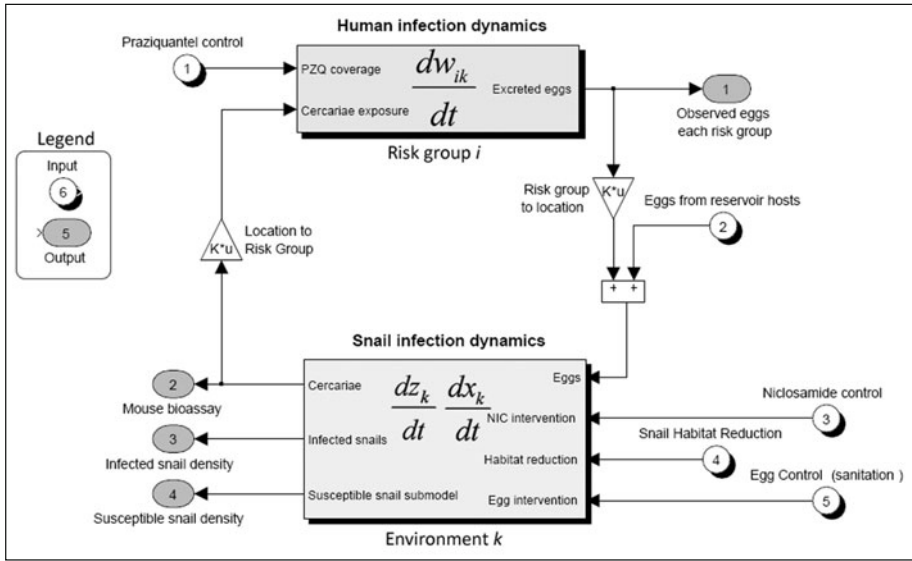


Figure 1. Diagram illustrating the structure of a multi-risk group model incorporating field data as both inputs and outputs. The host population is divided into  $i$  groups and the environment partitioned into  $k$  environments.

etc.<sup>33</sup> Environment refers to the land in which a risk group lives and farms. Hence, for each occupational group,  $i$ , living in environment  $k$ , the mean worm burden is given by the solution of the state equation:

$$\frac{dw_{ik}}{dt} = \alpha e^{-\mu_w \tau_w} S_i(t - \tau_w) \gamma_{ik} C_k(t - \tau_w) f(w_{ik}) - \mu_w w_{ik}(t) \quad (1.1)$$

where

$S_i(t)$  is the water exposure index of occupation group  $i$  and reflects the seasonal variation in water contact;

$e^{-\mu_w \tau_w}$  is the fraction of worms surviving the development time in humans;

$\alpha$  is the number of parasites acquired per cercaria per  $m^2$  skin surface contact;

$f(w_{ik})$  is the density dependent worm establishment function which describes a process in which the likelihood of developing into an adult worm is assumed to be reduced when the worm burden is high due to a 'crowding effect', to concomitant immunity, or both;

$\mu_w$  is the worm mortality rate; and

$C_k(t - \tau_w)$  is the mean spatial density of cercariae in irrigation system  $k$  at time  $t - \tau_w$ . The time delay is due to the fact that the rate of change in the number of adult worms at time  $t$  is due to exposure to cercariae at time  $t - \tau_w$  where  $\tau_w$  is the worm development period in human hosts.

### Modelling Cercariae-Environment Interactions

Cercariae are the free-living aquatic stage of the parasite which can infect humans and other mammals. They are negatively geotrophic and positively phototropic, thus cercariae accumulate at the surface of water where they seek an appropriate mammalian host. They are highly susceptible to environmental stressors, including desiccation, turbulence in the water column, water temperature, aquatic chemistry and light.<sup>2,35-39</sup> Water temperature and flow are key determinants

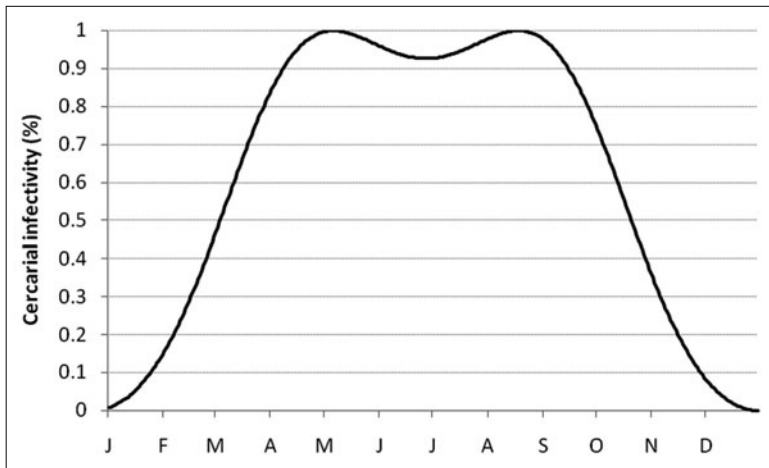


Figure 2. Daily cercarial infectivity for one year (2004) in Shian 5 as determined by water temperature following Upatham et al.<sup>35</sup>

of cercarial viability and thus  $C_k(t)$  is dependent on the infected snail population as modified by these environmental factors:

$$C_k(t) = I_c(T_1) \frac{r_c(t)}{A_s} \sigma A_b z_k(t) \quad (1.2)$$

where

- $I_c(T_1)$  is the temperature-dependent infectivity of cercariae, described below;
- $T_1$  is the surface water temperature, measured directly using an automated logger, or estimated from air temperature using a model described below; and
- $A_s$  is the nominal surface water area of the village irrigation system;
- $r_c(t)$  the precipitation-and/or irrigation-dependent modulation of the average daily cercarial production [ $\sigma A_b z_k(t)$ ] which enters the aquatic environment, defined briefly below and in detail elsewhere;<sup>40</sup>
- $\sigma$  is the cercarial production per infected snail per day;
- $A_b$  is the area of snail habitat;
- $z_k(t)$  is the infected snail density.

### **Temperature-Dependent Cercarial Activity**

Cercarial activity, including host-seeking, surface seeking, host penetration and survival are known to be temperature sensitive. Experiments that examine the influence of temperature on successful penetration and establishment in animal hosts reveal the combined effect of temperature on multiple activities.<sup>35</sup> Cercariae exposed to temperatures between 15 and 30 degrees C show the highest worm recovery rates from mouse hosts. Above and below this range, recovery rates decrease, resulting in the annual infectivity cycle depicted in Figure 2 using temperature data for the Shian 5 study village in 2004. This relationship is incorporated in the model as  $I_c(T_1)$ , the temperature-dependent infectivity of cercariae, serving as one source of seasonal limitation of transmission in the framework presented here.

### **Flow-Dependent Cercarial Activity**

Cercarial production is modulated by the availability of water in channels,  $r_c(t)$ , which can be predicted from precipitation and temperature using a conceptual rainfall-runoff model, IHACRES,<sup>41,42</sup> described elsewhere<sup>40</sup> and modeled following the simple binary formulation:

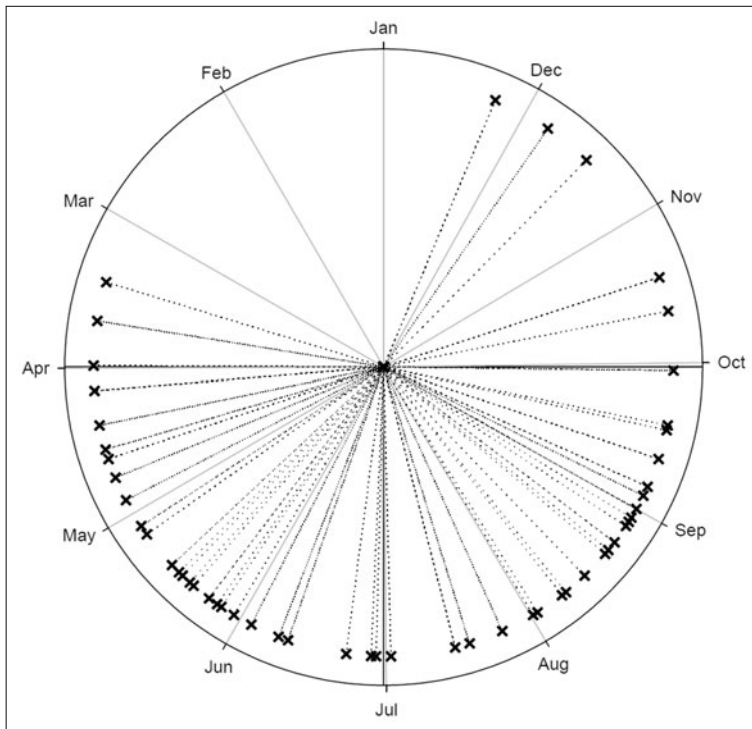


Figure 3. Polar plot of annual (2003) daily water flow classifications as predicted by the IHACRES hydrological model. Symbols (x) represent “transmission days,” days with sufficient channel flow to allow for egg hatching and the coincidence of water contact and cercariae. Reprinted with permission from: Remais J, Liang S, Spear RC, Environ Sci Technol 2008; 42(7):2643-2649. © 2008 American Chemical Society.

$$r_c(t) = \begin{cases} 0 & q_t < \Omega_c \\ 1 & q_t \geq \Omega_c \end{cases} \quad (1.3)$$

where  $q_t$  is the normalized, IHACRES-predicted channel discharge at time step  $t$ ; and  $\Omega_c$  is the discharge threshold for cercarial release. If flow falls below the threshold for cercarial release, then  $r_c(t) = 0$ , effectively prohibiting cercarial penetration of hosts. When the flow threshold is met or exceeded,  $r_c(t) = 1$  and transmission proceeds unimpeded. Thus, during and after rain events, when flowing water is available, cercarial dispersion and penetration can occur. This formulation is consistent with the ecology of *Oncomelania* snails, which reside above the waterline but are submerged and shed cercariae when channel flows rise.<sup>43</sup> A sample classification of daily  $r_c(t)$  in one study site for the year 2003 is given in Figure 3.

### Modelling Snail-Environment Interactions

Models of schistosome intermediate hosts have typically explored a limited number of functional forms and environmental variables, such as Woolhouse and Chandiwana<sup>44</sup> and Woolhouse,<sup>45</sup> who selected simple nonlinear models relating water temperature and *B. globosus* recruitment and linear models relating mortality and water temperature. Woolhouse and Chandiwana<sup>46</sup> adapted their previous model<sup>44</sup> for flowing water environments, adding the effect of high rainfall. In contrast to the intermediate hosts of African schistosomes, modelling of the *Oncomelania hupensis* host of *S. japonicum* is rare.



*O. hepensis* snails are amphibious, inhabiting irrigation canals, riparian zones and littoral environments. The vegetation in these sites serves to maintain a suitable microenvironment, including temperature and humidity, as well as providing food and refuge resources. Juveniles are submerged during early stages of development, while adults are often found above the water line on vegetation and on shaded moist soil. Adults persist under environmental stress by closing their shell opening with a maneuverable operculum, allowing for aestivation and making them somewhat resistant to dry conditions.<sup>47,48</sup>

Liang et al<sup>33</sup> previously used a temperature-dependent recruitment model coupled with constant annual mortality to model seasonal abundance fluctuations of *O. hepensis*, but no direct measurements of recruitment, mortality or environmental variables were made to construct this model. Others have shown that *O. hepensis* is highly sensitive to seasonal weather conditions including flooding, temperature and humidity.<sup>5,43</sup> In response to these sensitivities, another study<sup>49</sup> used a mark-recapture technique to directly measure birth and mortality processes under changing environmental conditions, finding temperature and heavy precipitation to be most influential in determining abundance. A validated population model for *O. hepensis* was presented, suitable for predicting snail abundance in changing environments. In this model, the susceptible snail state equation is defined as:

$$\frac{dx_k}{dt} = g\left(t - t_x, \bar{E}_{t-t_x}\right)x_k(t - t_x) - b\left(t, \bar{E}_t\right)x_k(t) \quad (1.4)$$

where population gains in environment  $k$  are accomplished by the recruitment term  $g\left(t - t_x, \bar{E}_{t-t_x}\right)$ , lagged by a temperature-dependent development time,  $t_x$ , required to reach mature size (estimated for *O. hepensis* elsewhere<sup>50</sup>) and losses are accounted for by mortality term  $b\left(t, \bar{E}_t\right)$ , where  $\bar{E}_t$  is a vector of environmental variables at time  $t$ . Submodels  $g$  and  $b$  are defined as follows, with model fitting and parameters described in detail elsewhere:<sup>49</sup>

$$g\left(t - t_x, \bar{E}_{t-t_x}\right) = \beta_1 e^{-0.5 \left[ \log\left(\frac{T(t-t_x)}{\beta_2}\right) / \beta_3 \right]^2} + \beta_4 e^{-0.5 \left[ \frac{R(t-t_x) - \beta_5}{\beta_6} \right]^2} \quad (1.5)$$

where  $T(t - t_x)$  is air temperature and  $R(t - t_x)$  is a count of rain events >15 mm per month at time  $t - t_x$  and  $\beta_{1-6}$  are fit parameters; and

$$b\left(t, \bar{E}_t\right) = \delta_1 + 4\delta_2 \frac{e^{\left[ \frac{T(t) - \delta_3}{\delta_4} \right]}}{\left( 1 + e^{\left[ \frac{T(t) - \delta_3}{\delta_4} \right]} \right)^2} + \delta_5 R(t) \quad (1.6)$$

where  $T(t)$  is air temperature,  $R(t)$  is a count of rain events >15 mm per month and  $\delta_{1-5}$  are fit parameters.

Fits of submodels  $g$  and  $b$  to environmental data are shown in Figure 4. Notice that the susceptible snail state equation is not dependent on other, endogenous transmission model state variables. Consequently, the susceptible snail model can be calibrated independent of the full transmission model, thus economizing the computation required for calibration, described further in the chapter by Spear and Hubbard in this volume.

State variable  $z_k(t)$ , the density of infected snails in environment  $k$ , is given by the solution to:

$$\frac{dz_k}{dt} = \rho e^{-\mu_z \tau_z} \xi(T_1) M_k(t - \tau_z) x_k(t - \tau_z) - \mu_z z_k \quad (1.7)$$

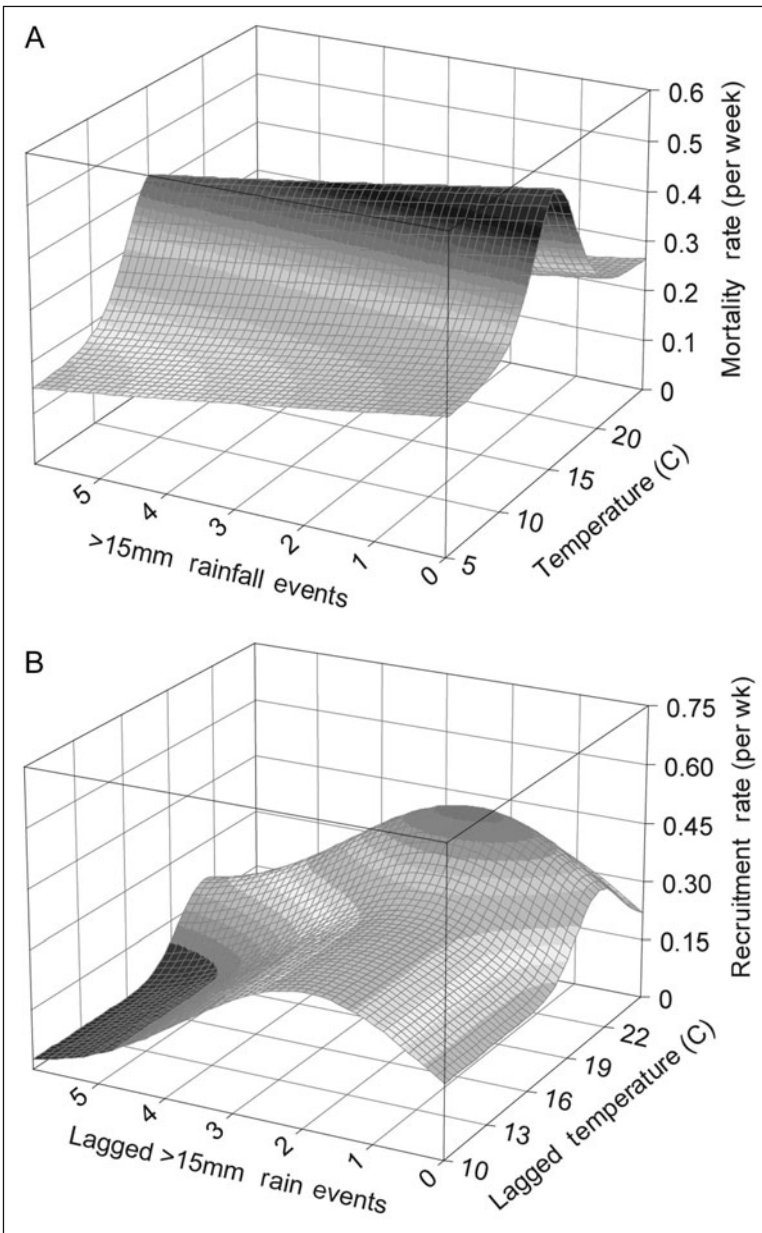


Figure 4. A) Relationship between instantaneous per capita recruitment rate for *O. hupensis robertsoni* and mean air temperature and mean number of rainfall events >15 mm (month<sup>-1</sup>). Climate data are lagged by  $t_i$  as discussed elsewhere.<sup>49</sup> B) Relationship between instantaneous per capita mortality rate for *O. hupensis robertsoni* and mean air temperature and mean number of rainfall events >15 mm (month<sup>-1</sup>). Reprinted with permission from: Remais J, Hubbard A, Wu Z, Spear R. J Appl Ecol 2007; 44(4):781-791. © 2007 Blackwell Publishing Ltd.

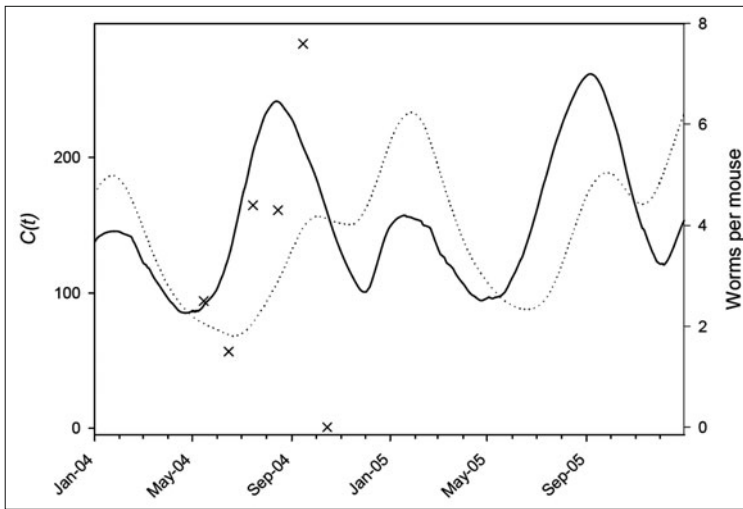


Figure 5. Mean of 1000 simulated predictions of daily cercarial output in a simulated village (Shian 5) generated using the temperature- and precipitation-driven snail model (—) of Remais et al.<sup>49</sup> and the model (····) used by Liang et al.<sup>33</sup> Symbols (x) are mean worms recovered from mice ( $n = 94$ ) deployed in 2001 in Shian 5 as reported by Spear et al.<sup>52</sup>

where

$x_k(t)$  is the density of susceptible snails in environment  $k$ ;

$\rho$  is the fraction of those miracidia which successfully infect snails;

$\xi$  is a parameter representing the degree of spatial convergence of the distribution of snail hosts and miracidia;

$\mu_z$  is the mortality rate of infected snails; and

$M_k(t)$  is the mean density of miracidia in the irrigation system in environment  $k$ , derived from hatched eggs, a process described below.

The implications of an environmentally-driven snail model are shown in Figure 5 using a transmission model previously calibrated for Shian 5, described in detail elsewhere<sup>51</sup> and in the chapter by Spear and Hubbard in this volume. The spring snail population peak generated by the model leads to significant infected snail numbers earlier in the year when compared to the model used by Liang.<sup>33</sup> As a consequence, the onset of peak cercarial release into waterways is shifted back by more than a month, from late September to mid-August, a prediction that is in line with available cercarial concentration data from field studies in Shian 5.<sup>52</sup> Comparisons to field data of this sort can highlight how environmentally-driven intermediate host models can bring model performance into better agreement with real world observations.

### Modelling Ova-Environment and Miracidia-Environment Interactions

Total egg production from all risk groups is modeled as:

$$E_k(t) = \frac{1}{2}h \sum_i g_i n_i w_{i,k} \Phi(w_{i,k}, \kappa_{w_i}) \quad (1.8)$$

where

$h$  is eggs per gram stool (EPG) per worm pair based on Hubbard et al;<sup>53</sup>

$g_i$  is the average stool production of a member of the  $i$ th group;

$n_i$  is the number of people in  $i$ th group whose stool is used as fertilizer;

$\Phi(w_{i,k}, \kappa_{w_i})$  is worm mating probability following May<sup>54</sup> and described elsewhere.<sup>33</sup>

The factor  $\frac{1}{2}$  converts mean worm burden to worm pairs.

Before hatching into miracidia, excreted eggs are subject to environmental stress. They are resilient, however and can persist for days on fields before being washed into irrigation channels by a precipitation event.<sup>40</sup> A composite parameter representing on-field inactivation of eggs can be calculated from literature values of egg resilience and a simple first-order inactivation process can be used to express viable eggs,  $E^*(t)$ , as a function of the sum of decaying eggs contributed since the last flow event:<sup>40</sup>

$$E_k^*(t) = \sum_{T-\tau_E}^T E_k(t) e^{-\epsilon_d(T-t)} \quad (1.9)$$

where

$E_k^*(t)$  is the sum of viable eggs shed by infected humans in environment  $k$  since the last flow event;

$E(t)$  represents eggs excreted into environment, defined above;

$\epsilon_d$  is the decay constant governing inactivation of eggs lying dormant on fields between flow events;

$T - \tau_E$  is the time since last flow event.

Miracidia are short-lived, free-swimming and are drawn to light, accumulating near the surface of water where they seek an appropriate snail host. They are sensitive to water temperature and aquatic chemistry, with the former exerting a pronounced influence on viability.<sup>1,55-57</sup> Experimental data of the influence of temperature on miracidial infectivity have shown optimal activity between 15 and 30 degrees C,<sup>58</sup> a relationship incorporated into the model of the net effective density of miracidia in environment  $k$ ,  $M_k(t)$ , a function of viable eggs in the environment,  $E_k^*(t)$ :

$$M_k(t) = I_m(T_1) \frac{r_e(t)}{A_s} \beta E_k^*(t) \quad (1.10)$$

where

$I_m(T_1)$  is the surface water temperature dependent miracidial infectivity to snails analogous to  $I_c(T_1)$  discussed above for cercariae;

$A_s$  is the nominal surface water area of the village irrigation system;

$r_e(t)$  is the precipitation-and/or irrigation-dependent modulation of the average daily miracidial production [ $\beta E(t)$ ] which enters the aquatic environment, defined briefly below and in detail elsewhere;<sup>40</sup>

$\beta$  is the fraction of the total daily egg production of infected villagers returned into the environment as fertilizer, adjusted for the presence of sanitation.

Flow events provide opportunities for viable eggs to hatch and I therefore define  $r_e(t)$  analogous to the cercarial equation at time  $t$  as:

$$r_e(t) = \begin{cases} 0 & q_t < \Omega_e \\ 1 & q_t \geq \Omega_e \end{cases} \quad (1.11)$$

where  $q_t$  is the normalized, IHACRES-predicted discharge at time step  $t$ , as above. Here, if water flow falls below the threshold for egg hatching,  $\Omega_e$ ,  $r_e(t) = 0$  and eggs lie dormant. When the flow threshold is met or exceeded,  $r_e(t) = 1$  and viable eggs on fields are washed into the irrigation system, where they hatch and can infect snails.

## Model Parameters

The model was structured and parameterized to allow the use of as much of the field data as can be feasibly collected with the methods available in rural China. This includes environmental data (described below), cross-sectional data on snail population density, seasonally varying water contact patterns by group and survey data on the intensity of human infection. Some of these data are inputs to the model and some are used for parameter estimation. The issue of parameter

**Table 2. Parameter ranges and environmental inputs for transmission model following Liang et al.<sup>51</sup> The distribution for all parameters is uniform except for log-uniform distribution for  $\alpha$ ,  $\rho$  and  $\gamma_s$ . Data estimates marked \* are available in Table 4 in Liang et al.<sup>51</sup>**

Parameters	Interpretation and Unit	Ranges	References
<b>Biological</b>			
$\tau_w$	Development time of worms in human host (day)	20-40	59
$\mu_w$	Worm natural mortality (/day)	0.000183-0.0014	59
$h$	Eggs excreted (/worm pair/gram feces)	0.768-2.72	53
$\mu_z$	Patent and latent snail death rate (/day)	0.0063-0.033	60
$\sigma$	Cercarial production (/sporocyst/day)	20-50	61,62
$h_{PZQ}$	Efficacy of praziquantel	0.8-0.95	63,64
$D_{D1}$	Degree-days for sporocyst development	1550-1950	65
$T_{D1}$	Threshold temperature for sporocyst development (°C)	12-15	62
$\alpha$	Schistosome acquired (/cercaria/m <sup>2</sup> contact)	0.0001-0.5	-
$\rho$	Intermediate host infection (/miracidium/m <sup>2</sup> surface water)	0.000001-0.0005	-
$\beta_{1-6}$	Intermediate host recruitment parameters	See ref	49
$\delta_{1-5}$	Intermediate host mortality parameters	See ref	49
<b>Site-specific</b>			
$w_{0i}$	Initial worm burden in the $i$ th group	Data estimate*	Local data
$Z_0$	Initial density of infected snails	Data estimate*	Local data
$S_i(t)$	Water contact index	Data estimate*	Local data
$x_0$	Initial density of susceptible snails	Data estimate*	Local data
$\kappa_{0i}$	Initial worm aggregation parameter	Data estimate*	Local data
$x_0$	Initial mean snail density	17-35	66
$\gamma_i$	Spatial index for the distribution and interaction between exposure and cercariae for $i$ th group	Data estimate*	Local data
$\xi$	Spatial index for the distribution and interaction between snails and miracidia	1	-
<b>Inputs</b>			
$T_1$	Water temperature (°C)	No constraint	Local data
$T_2$	Snail microenvironment temperature (°C)	No constraint	Local data
$C_{chemo}$	Chemotherapy coverage	Data estimate*	Local data
$P$	Rainfall (mm/day)	No constraint	Local data
$r(t)$	Precipitation-driven channel flow (binary)	Data estimate	40

estimation is complex but central to our approach. Table 2 lists parameter values for the model and their literature sources. When used to study interventions (discussed in detail in the chapter by Seto and Carlton in this volume), a fundamental challenge is to reduce the residual uncertainty

in model output, or its behavior more broadly, after as much of the local data as possible has been utilized to narrow the posterior distributions of the parameter values (see chapter by Spear and Hubbard in this volume).

To that end, we have conducted a variety of field studies to better understand the importance of certain elements of the model, or to obtain parameter estimates relevant to the biology of the snail or parasite specific to the region in which we work. Examples are the value of the parameter describing the production of parasite eggs per mated worm pair per gram of stool,<sup>53</sup> the importance of rainfall in determining infected snail densities and the concentration of cercariae in irrigation water.<sup>52</sup> There is no question that the modelling approach, with the ultimate objective of designing effective intervention strategies to meet public health objectives, has led us to seek quantitative estimates of factors controlling disease transmission that have not been of great interest to Asian parasitologists since the work of Pesigan.<sup>67</sup>

## Environmental Data

Modelling the environmental drivers of seasonality requires an accurate dataset of environmental variables, acquired by measurement where possible and prediction where not. As in all environmental monitoring, strict quality assurance measures need be taken, including instrument calibration/certification, statistically valid sampling designs, reference sites and data verification.<sup>68,69</sup> In the work described here, air temperature, barometric pressure and relative humidity are collected relatively easily throughout the study region using continuous loggers (Hobo Onset H21-002) sampling at 12 minute intervals, validated with regional data available from the National Climatic Data Center.<sup>70</sup> Likewise, water temperature and water column height (stage) are logged at the same interval using similar equipment (Hobo Onset U20-001-01, U22-01) in a representative sample of irrigation channels. To estimate flow ( $\text{m}^3 \text{s}^{-1}$ ) from stage (m) in these channels, flow measurements must be made at multiple flow volumes in order to construct a simple rating curve. Daily precipitation is collected using a combination of tipping gauges (Hobo Onset RG3-M) and manually read rain gauges. Where data were missing due to equipment or staff error (typically accounting for <1 percent of data points in the study), data were obtained from the NOAA weather station located at the Xichang municipal airport (World Meteorological Organization ID 56571), approximately 13 km from the study sites. Where water temperature was not directly measured, it was estimated from air temperature using a standard, simple linear model:<sup>71</sup>

$$T_w(t) = \alpha + \beta T_a(t) \quad (1.12)$$

where  $T_w$  = water temperature,  $T_a$  = air temperature and  $\alpha$  and  $\beta$  are fit parameters. Time lags were excluded from the model as the observed lags (<4 hours) were much shorter than the averaging period (1 day), as is typical for temperature predictions in shallow channels.<sup>72</sup>

## Model Dynamics

The model described above, when parameterized as described in the chapter by Spear and Hubbard, generates predictions of the sort depicted in Figure 6. Mean worm burdens for the three risk groups in Shian 5 are summarized for 1000 simulations over the five year period 2001-2005. The impact of two chemotherapies, modeled as described in the chapter by Seto and Carlton in this volume, is shown in the Figure. One characteristic that can be explored using this simulation environment is the time-to-return for worm burdens after chemotherapy. As is evident in the plot, worm burden returns to precontrol levels in the farmer group in less than 3 years, while the student and other group require considerably more time to rebound, owing to their differing exposure profiles.

The seasonal rise in worm burden following the second simulated chemotherapy can be seen in Figure 7 which plots the acquisition (or loss by mortality) of worms in the three risk groups. Note that the acquisition of new worms in the Figure represents exposures to cercariae that took place as many as 6 weeks prior. Notable is the bimodal farmer pattern which results from exposures during the spring planting season. While similar activities occur during the late winter and early spring during the harvest of the winter crop, cercarial shedding and infectivity is limited in this period due to

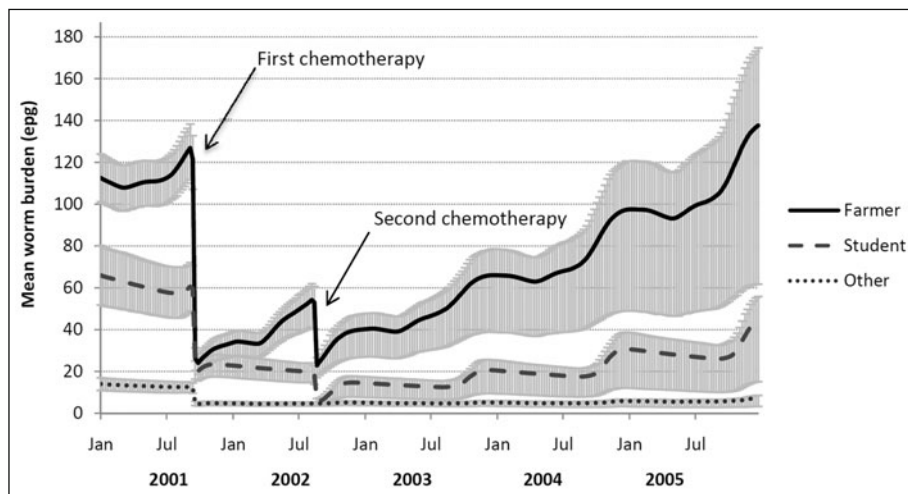


Figure 6. A 5-year prediction of 1000 simulated time profiles (line: mean; envelope: 25th and 75th percentiles) of mean worm burden for each of the three risk groups in Shian 5 following two chemotherapies (coverage based on field data).

low temperatures and limited precipitation. During the spring planting, however, temperatures just exceed the limits for cercarial activity and spring rains provide opportunities for the coincidence of cercariae and water contact. The timing and nature of interventions can be selected based on these seasonal patterns, as described in the chapter by Seto and Carleton in this volume.

All three risk groups experience a 'shut-down' of worm acquisition in the late fall related to the coincidence of temperature decreases, lower snail numbers and reduced water contact activities. The time-varying  $I(T)$ ,  $r(t)$  and  $s(t)$  terms are at their minimum values in the late fall through winter and 'turn on' again in the spring, remaining 'on' through the transmission season. Of great interest is to explore the effects of these gating functions<sup>73</sup> on the transmission process and their sensitivity

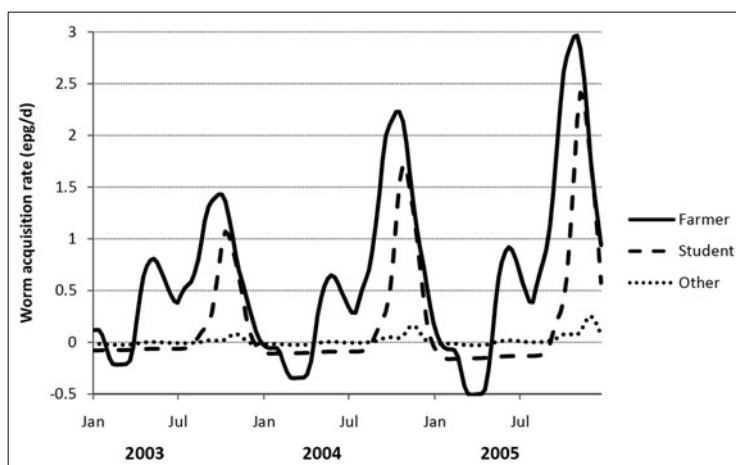


Figure 7. The derivative of worm burdens following the second chemotherapy in Figure 6, representing the rate of worm acquisition or loss (expressed as epg/d).



to local and regional environmental changes. Furthermore, efforts are needed to extend the model to account not just for environmental variables, but for their spatial distribution.

## Modelling Spatial Connectivity

Human schistosomes are model organisms for the study of and response to, the spread of disease in space and time, as their transport through the environment takes place along discrete pathways. Parasites are carried in advective flows along canals and streams as both larvae and ova. Within intermediate snail hosts, parasites are conveyed among and between aquatic and riparian habitats and as adult worms, human and animal hosts serve as the transport mode. With respect to the *S. japonicum* parasite, I term these flows parasite diffusion, using the phrase to encompass all diffusive pathways along which parasites are transported into new and existing locales. The presence of suitable pathways can affect the probability of emergence of transmission, the level of worm burden within a community once transmission is established and how transmission spreads to neighboring areas. What is more, the degree to which an endemic or emergent community is connected can have important implications for the efficacy and sustainability of various control strategies.

In a preliminary exploration of parasite diffusion, the travel time of the free-swimming forms of the parasite or snail larvae due to advective transport in typical irrigation systems was estimated,<sup>74</sup> showing empirically that there is significant transport of viable parasite larvae within irrigation channels and that transport of larval stages occurs over considerable distance, with viable organisms detectable as far as 400 m from source snails.<sup>38</sup> Using these key transport parameters in a follow-up project, the impact of larval transport on endemic disease transmission was assessed using a spatial-temporal model of networked villages,<sup>75</sup> showing that diffusion of larvae via the surface water pathway, on its own, influences not just the intensity of transmission in a village, but also the effectiveness of standard interventions. Such a model allows us to better understand a number of phenomena specific to the endemic situation, such as which villages serve as “sinks” in the network, villages where worm burden can accumulate because they lie at the bottom of a watershed of numerous connected upstream villages.

The implications of a connected landscape have been explored extensively in ecology, where metapopulation models<sup>76</sup> describe the effect of migration between connected patches on population conservation. Likewise, environmental and social connections can promote the persistence of schistosomiasis and challenge efforts to control transmission. While hydrological connectivity is relatively straightforward to characterize, social connectivity is considerably more difficult to measure and express mathematically. The indirect transmission of schistosomiasis differs from recent epidemiological modelling of social connectivity and contact networks for communicable disease spread.<sup>77–83</sup> Within the context of the endemic transmission situation, small-scale human mobility can spread parasites from village to village. This effect may be small though in comparison to other social behaviors, such as the renting or selling of water buffalo which, if infected, can potentially release much larger numbers of eggs into the environment. While these factors might be modeled much like hydrological connectivity over the small scale via inter-village flows, they differ from the hydrological situation in that these processes can occur over much larger spatial scales and much less predictably. While difficult to estimate precisely, we look to future field data to inform the probabilities that define the movements of heterogeneous hosts; much theoretical and empirical work is needed in this area.

## Extending the Modelling Framework

Our current research attention has shifted from endemic disease to disease re-emergence, a phenomenon we have documented in the mountainous region of Sichuan Province.<sup>84</sup> For studying re-emergence, human infection may be more appropriately modeled by risk groups with stochastic parasite establishment in a heterogeneous environment. The simplest form would be a stochastic compartmental model, where the risk group structure would be maintained with each compartment being comprised of a number of identical individuals. However, the



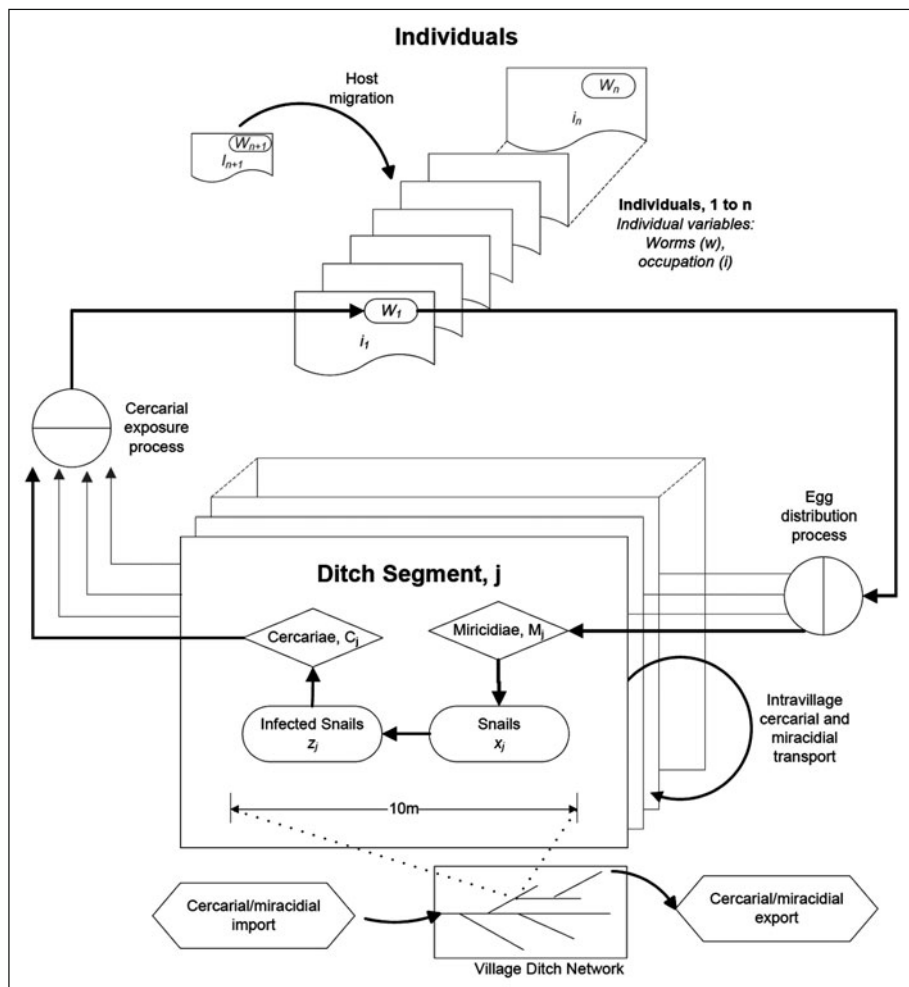


Figure 8. A diagrammatic conceptualization of the re-emergence model. The frame of reference of the flowchart is the interaction of one individual with the ditch environment. Stochastic introduction processes include host migration and import of cercariae and miracidiae, while cercarial exposure, egg distribution and hydrologic transport processes are implemented on a spatially-explicit, segmented mapping of the ditch environment.

static representation of the aggregation of parasites in humans in the deterministic model, even within our risk groups, does not translate easily to the re-emergent situation where, initially, the population is parasite-free. Hence, an individually-based model is preferred.<sup>31</sup> Individual-based micro-simulation models have been utilized in studying schistosomiasis transmission in endemic settings, but without our emphasis on environmental factors.<sup>85</sup> In ecology there has also been considerable interest in individually-based models.<sup>86</sup> There, the analog to our discrete population of humans is a population of animals in a heterogeneous, but continuous environment. There are particularly interesting approaches being explored which might allow us to naturally utilize our GIS data base and GPS-based maps in an individually-based model.<sup>87</sup>

Figure 8 schematically represents the elements of a new model in which the stochastic introduction of parasites is implemented by means of migration of infected hosts and advective parasite transport. Heterogeneous ditch environments, then, serve as platforms wherein eggs are released from infected individuals who, along with uninfected individuals, traverse the waterway environments and are potentially infected by contact with cercarial contaminated water. Stochastic implementations of the egg release and cercarial exposure processes are particularly suitable for a system where transmission is strongly conditioned by both environmental and behavioral factors that defy deterministic formulation. Moreover the stochastic model proposed here provides the structure to capture the potentially large influence of chance events that have been recognized to govern early epidemic dynamics, even in relatively large populations.<sup>88-90</sup>

## Conclusion

The wide array of processes discussed herein can be conceptualized at various spatial and temporal scales, evaluated for their relative abilities to capture relevant transmission dynamics, including seasonal dynamics, and incorporate available field data. Measuring the potential drivers of seasonality may be relatively straightforward in the case of climate, but measuring and formalizing patterns of human behavior, particularly in a spatially explicit context, remain formidable challenges.<sup>91</sup> Indeed, iterative evaluation of alternative models in the light of field data is the essence of the modelling process in our application. Ultimately, quantifying and synthesizing the interaction between environmental and social determinants in transmission models offers great promise for developing novel modes of control in diverse environments.

## References

1. Anderson RM, Mercer JG, Wilson RA et al. Transmission of *Schistosoma-mansoni* from man to snail—experimental studies of miracidial survival and infectivity in relation to larval age, water temperature, host size and host age. *Parasitology* 1982; 85:339-360.
2. Upatham E. Effect of a waterfall on the infectivity of *St. Lucian Schistosoma mansoni* cercariae. *Trans R Soc Trop Med Hyg* 1973; 67(6):884-885.
3. Riley S, Carabin H, Ne et al. Multi-Host transmission dynamics of *Schistosoma japonicum* in Samar Province, the Philippines. *PLoS Medicine* 2008; 5(1):e18.
4. Davis GM, Wu WP, Chen HG et al. A baseline study of importance of bovines for human *Schistosoma japonicum* infections around Poyang Lake, China: Villages studied and snail sampling strategy. *Am J Trop Med Hyg* 2002; 66(4):359-371.
5. Zhou XN, Wang TP, Wang LY et al. The current status of schistosomiasis epidemics in China. *Zhonghua Liu Xing Bing Xue Za Zhi* 2004; 25(7):555-558.
6. Wang RB, Wang TP, Wang LY et al. Study on the re-emerging situation of schistosomiasis epidemics in areas already under control and interruption. *Zhonghua Liu Xing Bing Xue Za Zhi* 2004; 25(7):564-567.
7. W.H.O. Prevention and control of schistosomiasis and soil-transmitted helminthiasis: Report of a W.H.O expert committee, 2001.
8. Sleight A, Li X, Jackson S et al. Eradication of schistosomiasis in Guangxi, China. Part 1: Setting, strategies, operations and outcomes, 1953-92. *Bull World Health Organ* 1998; 76(4):361-372.
9. W.H.O. Parasitic diseases in water resources development: The need for intersectoral negotiation. Geneva: World Health Organization, 1993.
10. Steinmann P, Keiser J, Bos R et al. Schistosomiasis and water resources development: systematic review, meta-analysis and estimates of people at risk. *The Lancet Infectious Diseases* 2006; 6(7):411-425.
11. Sero EYW, Wu W, Liu H-Y et al. Impact of changing water levels and weather on oncomelania hupensis hupensis populations, the snail host of *Schistosoma japonicum*, downstream of the three Gorges dam. *EcoHealth* 2008; in press.
12. Jobin W. Dams and Disease: Ecological Design and Health Impacts of Large Dams, Canals and Irrigation Systems. London: Routledge, 1999.
13. Pascual M, Dobson A. Seasonal patterns of infectious diseases. *PLoS Med* 2005; 2(1):e5.
14. Pascual M, Bouma MJ, Dobson AP. Cholera and climate: Revisiting the quantitative evidence. *Microbes Infect* 2002; 4(2):237-245.
15. Kendall BE, Briggs CJ, Murdoch WW et al. Why do populations cycle? A synthesis of statistical and mechanistic modeling approaches. *Ecology* 1999; 80:1789-1805.

16. Altizer S, Dobson A, Hosseini P. Seasonality and the dynamics of infectious diseases. *Ecological Letters* 2006; 9(4):467-484.
17. Thomas CJ, Hay SI. Global climate change and malaria—Authors' reply. *The Lancet Infectious Diseases* 2005; 5(5):259-260.
18. Macdonald G. The dynamics of helminth infections, with special reference to schistosomiasis. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1965; 59(5):489-506.
19. Hairston NG. An analysis of age-prevalence data by catalytic models. A contribution to the study of bilharziasis. *Bull World Health Organ* 1965; 33(2):163-175.
20. Anderson RM, May RM. Helminth infections of humans—mathematical-models, population-dynamics and control. *Advances in Parasitology* 1985; 24:1-101.
21. Barbour AD. Modeling the transmission of schistosomiasis: An introductory view. *American Journal of Tropical Medicine and Hygiene* 1996; 55(5):135-143.
22. Chan MS, Guyatt HL, Bundy DAP et al. The Development of an age-structured model for schistosomiasis transmission dynamics and control and its validation for *Schistosoma mansoni*. *Epidemiology and Infection* 1995; 115(2):325-344.
23. Chan MS, Bundy DAP. Modelling the dynamic effects of community chemotherapy on patterns of morbidity due to *Schistosoma mansoni*. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1997; 91(2):216-220.
24. Feng Z, Li CC, Milner FA. Schistosomiasis models with density dependence and age of infection in snail dynamics. *Math Biosci* 2002; 177-178:271-286.
25. Gryseels B. Uncertainties in the epidemiology and control of schistosomiasis. *American Journal of Tropical Medicine and Hygiene* 1996; 55(5 Suppl):103-108.
26. Woolhouse ME, Hasibeder G, Chandiwana SK. On estimating the basic reproduction number for *Schistosoma haematobium*. *Tropical Medicine and International Health* 1996; 1(4):456-463.
27. Woolhouse MEJ. On the application of mathematical models of schistosome transmission dynamics .1. natural transmission. *Acta Tropica* 1991; 49(4):241-270.
28. Woolhouse MEJ. Mathematical models of transmission dynamics and control of schistosomiasis. *American Journal of Tropical Medicine and Hygiene* 1996; 55(5):144-148.
29. Yu JM, Yuan HC, J YQ et al. A transmission model for schistosomiasis japonica in lake Marchlands region. *Chinese Journal of Public Health* 1998; 17(6):347-350.
30. Williams GM, Sleight AC, Li Y et al. Mathematical modelling of schistosomiasis japonica: Comparison of control strategies in the People's Republic of China. *Acta Tropica* 2002; 82(2):253-262.
31. Koopman JS, Jacquez G, Chick SE. New data and tools for integrating discrete and continuous population modeling strategies. *Ann N Y Acad Sci* 2001; 954:268-294.
32. Chan MS. The consequences of uncertainty for the prediction of the effects of schistosomiasis control programmes. *Epidemiology and Infection* 1996; 117(3):537-550.
33. Liang S, Maszle D, Spear RC. A quantitative framework for a multi-group model of schistosomiasis japonicum transmission dynamics and control in Sichuan, China. *Acta Trop* 2002; 82(2):263-277.
34. Spear RC, Seto E, Liang S et al. Factors influencing the transmission of *Schistosoma japonicum* in the mountains of Sichuan Province of China. *Am J Trop Med Hyg* 2004; 70(1):48-56.
35. Upatham ES, Kruatrachue M, Khunborivan V. Effects of physicochemical factors on the infection of mice with *Schistosoma japonicum* and *S. mekongi* cercariae. *Southeast Asian J Trop Med Public Health* 1984; 15(2):254-260.
36. Radke MG, Ritchie LS, Rowan WB. Effects of water velocities on worm burdens of animals exposed to *Schistosoma mansoni* cercariae released under laboratory and field conditions. *Exp Parasitol* 1961; 11:323-331.
37. Webbe G. The effect of water velocities on the infection of animals exposed to *Schistosoma mansoni* cercariae. *Ann Trop Med Parasitol* 1966; 60(1):78-84.
38. Lowe D, Xi J, Meng X et al. Transport of *Schistosoma japonicum* cercariae and the feasibility of niclosamide for cercariae control. *Parasitol Int* 2005; 54(1):83-89.
39. Jewsbury J. Effects of water velocity on snails and cercariae. *Parasitology Today* 1985; 1(4):116-117.
40. Remais J, Liang S, Spear RC. Coupling hydrologic and infectious disease models to explain regional differences in schistosomiasis transmission in Southwestern China. *Environ Sci Technol* 2008; 42(7):2643-2649.
41. Jakeman AJ, Hornberger GM. How much complexity is warranted in a rainfall-runoff model. *Water Resources Research* 1993; 29(8):2637-2649.
42. Jakeman AJ, Littlewood IG, Whitehead PG. Computation of the Instantaneous unit-hydrograph and identifiable component flows with application to 2 small upland catchments. *Journal of Hydrology* 1990; 117(1-4):275-300.
43. Pesigan TP, Farooq M, Hairston NG. Studies on *Schistosoma japonicum* infection in the Philippines. 2. The Molluscan Host. *Bulletin of World Health Organization* 1958; 18:481-578.

44. Woolhouse MEJ, Chandiwana SK. Population biology of the freshwater snail *bulinus-globosus* in the Zimbabwe highveld. *Journal of Applied Ecology* 1990; 27(1):41-59.
45. Woolhouse MEJ. Population biology of the freshwater snail *biomphalaria pfeifferi* in the Zimbabwe highveld. *Journal of Applied Ecology* 1992; 29(3):687-694.
46. Woolhouse ME, Chandiwana SK. Population dynamics model for *bulinus globosus*, intermediate host for *Schistosoma haematobium*, in river habitats. *Acta Trop* 1990; 47(3):151-160.
47. Rozendaal JA. Vector control. Methods for use by individuals and communities. Geneva: World Health Organization, 1997.
48. Davis GM, Wilke T, Zhang Y et al. Snail-Schistosoma, Paragonimus interactions in China: Population ecology, genetic diversity, coevolution and emerging diseases. *Malacologia* 1999; 41(2):355-377.
49. Remais J, Hubbard A, Wu Z et al. Weather-driven dynamics of an intermediate host: mechanistic and statistical population modelling of *oncomelania hupensis*. *Journal of Applied Ecology* 2007; 44(4):781-791.
50. Hong Q, Zhou X, Sun L et al. Impact of global warming on transmission of schistosomiasis in China. IV. Accumulated temperature for development of generations of *oncomelania hupensis* in natural environment. *Chinese Journal of Schistosomiasis Control* 2003; 15(4):269-271.
51. Liang S, Spear RC, Seto E et al. A multi-group model of *Schistosoma japonicum* transmission dynamics and control: Model calibration and control prediction. *Trop Med Int Health* 2005; 10(3):263-278.
52. Spear RC, Zhong B, Mao Y et al. Spatial and temporal variability in schistosome cercarial density detected by mouse bioassays in village irrigation ditches in Sichuan, China. *Am J Trop Med Hyg* 2004; 71(5):554-557.
53. Hubbard A, Liang S, Maszle D et al. Estimating the distribution of worm burden and egg excretion of *Schistosoma japonicum* by risk group in Sichuan province, China. *Parasitology* 2002; 125:221-231.
54. May RM. Togetherness among schistosomes—effects on dynamics of infection. *Mathematical Biosciences* 1977; 35(3-4):301-343.
55. Chernin E. Some host-finding attributes of *Schistosoma-mansoni* Miracidia. *American Journal of Tropical Medicine and Hygiene* 1974; 23(3):320-327.
56. Upatham ES. The effect of water temperature on the penetration and development of *St. Lucian Schistosoma mansoni* miracidia in local *biomphalaria glabrata*. *Southeast Asian J Trop Med Public Health* 1973; 4(3):367-370.
57. Donnelly FA, Appleton CC, Schutte CH. The influence of salinity on the ova and miracidia of three species of *Schistosoma*. *Int J Parasitol* 1984; 14(2):113-120.
58. Shao BR, Xu X. Artificial infection of schistosome on *oncomelania*. *Chinese Medical Journal* 1956; 42:357-372.
59. Anderson RM, May RM. *Infectious Diseases Of Humans: Dynamics And Control*. Oxford; New York: Oxford University Press, 1991.
60. Mac Kenzie WR, Schell WL, Blair KA et al. Massive outbreak of waterborne cryptosporidium infection in Milwaukee, Wisconsin: Recurrence of illness and risk of secondary transmission. *Clinical Infectious Diseases* 1995; (21):57-62.
61. Qian BZ, Qian J, Xu DM et al. The population dynamics of cercariae of *Schistosoma japonicum* in *oncomelania hupensis*. *Southeast Asian J Trop Med Public Health* 1997; 28(2):296-302.
62. Pesigan TP, Hairston NG, Jauregui JJ et al. Studies on *Schistosoma japonicum* infection in the Philippines. 2. The molluscan host. *Bulletin of World Health Organization* 1958; (18):481-578.
63. Stelma FF. Immuno-epidemiology, morbidity and chemotherapy in a community recently exposed to *Schistosoma mansoni* infection. A study in northern Senegal. (PhD Thesis), Rijksuniversiteit te Leiden, 1997.
64. Liang YS, Coles GC, Doenhoff MJ. Short communication: Detection of praziquantel resistance in schistosomes. *Tropical Medicine and International Health* 2000; 5(1):72-72.
65. Sun LP, Zhou XN, Hong QB et al. The preliminary study on the growing degree day (GDD) of *Schistosoma japonicum* development in the intermediate snail host, *oncomelania hupensis*. *Chinese Journal of Zoonoses* 2001; 17(4):80-82.
66. Zhao WX, Gu XG, Xu FS et al. An ecological observation of *oncomelania hupensis robertsoni* in Xichang, Daliang Mountains, Sichuan. *Sichuan Journal of Zoology* 1995; 14(3):119-121.
67. Pesigan TP, Farooq M, Hairston NG et al. Studies on *Schistosoma japonicum* infection in the Philippines. 1. General considerations and epidemiology. *Bull World Health Organ* 1958; 18(3):345-455.
68. US EPA. Guidance on choosing a sampling design for environmental data collection. Washington, DC: Government Printing Office, 2002.
69. US EPA. Guidance on environmental data verification and data validation. Washington, DC: Government Printing Office, 2002.
70. NOAA. Global hourly surface data: National oceanic and atmospheric administration, national climatic data center, 2008.
71. Stefan HG, Preud'homme EB. Stream temperature estimation from air temperature. *Water Resources Bulletin* 1993; 29(1):27-45.

72. Erickson TR, Stefan HG. Linear air/water temperature correlations for streams during open water periods. *Journal of Hydrologic Engineering* 2000; 5(3):317-321.
73. Liang S, Seto E, Remais J et al. Environmental effects on transmission and control of parasitic diseases exemplified by schistosomiasis in Western China. *Proc Natl Acad Sci USA* 2007; 104(17):7110-7115.
74. Maszle DR, Whitehead PG, Johnson RC et al. Hydrological studies of schistosomiasis transport in Sichuan Province, China. *Sci Total Environ* 1998; 216(3):193-203.
75. Xu B, Gong P, Seto E et al. A spatial-temporal model for assessing the effects of intervillage connectivity in schistosomiasis transmission. *Annals of the Association of American Geographers* 2006; 96(1):31-46, in press.
76. Hanski I. Habitat connectivity, habitat continuity and metapopulations in dynamic landscapes. *Oikos* 1999; 87(2):209-219.
77. Halloran ME, Longini IM Jr. Using validation sets for outcomes and exposure to infection in vaccine field studies. *Am J Epidemiol* 2001; 154(5):391-398.
78. Koopman JS, Chick SE, Simon CP et al. Stochastic effects on endemic infection levels of disseminating versus local contacts. *Math Biosci* 2002; 180:49-71.
79. Newman ME. Spread of epidemic disease on networks. *Phys Rev E Stat Nonlin Soft Matter Phys* 2002; 66(1 Pt 2):016128.
80. Sander LM, Warren CP, Sokolov IM et al. Percolation on heterogeneous networks as a model for epidemics. *Math Biosci* 2002; 180:293-305.
81. Grais RF, Ellis JH, Kress A et al. Modeling the spread of annual influenza epidemics in the US.: the potential role of air travel. *Health Care Manag Sci* 2004; 7(2):127-134.
82. Rvachev LA, Longini IM. A mathematical-model for the global spread of influenza. *Mathematical Biosciences* 1985; 75(1):1-1.
83. Sattenspiel L, Herring DA. Simulating the effect of quarantine on the spread of the 1918-19 flu in Central Canada. *Bull Math Biol* 2003; 65(1):1-26.
84. Liang S, Yang C, Zhong B et al. Re-emerging schistosomiasis in hilly and mountainous areas of Sichuan, China. *Bull World Health Organ* 2006; 84(2):139-144.
85. Vlas SJ, Van Oortmarssen GJ, Gryseels B et al. Schistosim: A microsimulation model for the epidemiology and control of schistosomiasis. *Am J Trop Med Hyg* 1996; 55(5 Suppl):170-175.
86. Grimm V. Ten years of individual-based modelling in ecology: What have we learned and what could we learn in the future? *Ecological Modelling* 1999; 115(2-3):129-148.
87. Bian L. The representation of the environment in the context of individual-based modeling. *Ecological Modelling* 2003; 159(2-3):279-296.
88. Lloyd-Smith JO, Galvani AP, Getz WM. Curtailing transmission of severe acute respiratory syndrome within a community and its hospital. *Proc R Soc Lond B Biol Sci* 2003; 270(1528):1979-1989.
89. Hufnagel L, Brockmann D, Geisel T. Forecast and control of epidemics in a globalized world. *Proc Natl Acad Sci USA* 2004; 101(42):15124-15129.
90. Riley S, Fraser C, Donnelly CA et al. Transmission dynamics of the etiological agent of SARS in Hong Kong: Impact of public health interventions. *Science* 2003; 300(5627):1961-1966.
91. Grassly NC, Fraser C. Seasonal infectious disease epidemiology. *Proc Biol Sci* 2006; 273(1600):2541-2550.